ATTACHMENT A
Remarks

Claims 1-16 stand pending in the present application. By this Amendment, Applicants have amended claims 1-16. Applicants respectfully submit that the present application is in condition for allowance based on the discussion which follows.

Claims 3-9 were rejected under 35 U.S.C. § 112, second paragraph. Applicants respectfully submit that claims 3-9 are not indefinite. The Examiner has alleged in essence that claim 3 is not consistent with dependent claim 4 alleging that claim 3 refers to a reaction of carboxylic acid (VI) with amino ester (VIII), where claim 4 refers to a reaction of an activated form of carboxylic acid (acid chloride) (VII) with the amino ester.

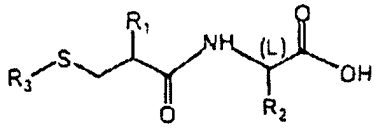
Contrary to what is implied by the Office Action, it should be stressed that claim 3 does not claim a "reaction" of a carboxylic acid with an amino ester, but a coupling of an acrylic acid with an amino ester so as to obtain the derivative of formula (V). This type of coupling is well known in the art and is generally referred to as "peptidic coupling", and one of ordinary skill in the art knows the means to be implemented in the scope of such a coupling. Further, steps (A1) and (A2) as defined in claim 4 actually correspond to a preferred embodiment of the coupling. It is in the spirit of this discussion that Applicants have amended claim 4 so as to make claim 4 more explicit as to this point.

Based on the foregoing discussion, Applicants respectfully submit that claims 3-9 are not indefinite and therefore respectfully request that the Examiner withdraw the rejection to claims 3-9 under 35 U.S.C. § 112, second paragraph.

Claims 1-16 were rejected under 35 U.S.C. § 102(b) as being anticipated by or in the alternative under 35 U.S.C. § 103(a) as being obvious over Greenberg et al, U.S. Patent No. 4,401,667 (hereinafter "the '667 patent") or Greenberg et al, U.S. Patent No. 4,474,799 (hereinafter "the '799 patent") (collectively referred to as "Greenberg").

The present invention as recited in clam 1 (currently amended) is directed to a process comprising performing a Michaël addition of a thiol acid onto compounds of formula (V) which are unsaturated esters (namely alkyl or phenylalkylene- esters, depending on the nature of the R3 group).

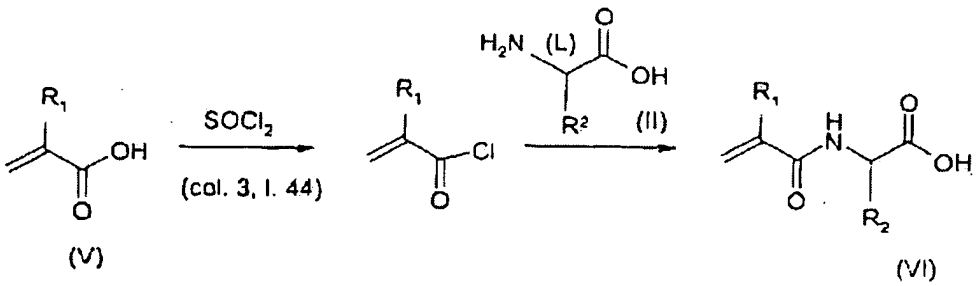
Greenberg does not disclose a Michaël addition of a thiol acid onto an ester of formula (V). On the contrary, both patents disclose, on column 3, a process for preparing enkephalinase inhibitors which implement the synthesis of a precursor (IV) which is depicted as:



(IV)

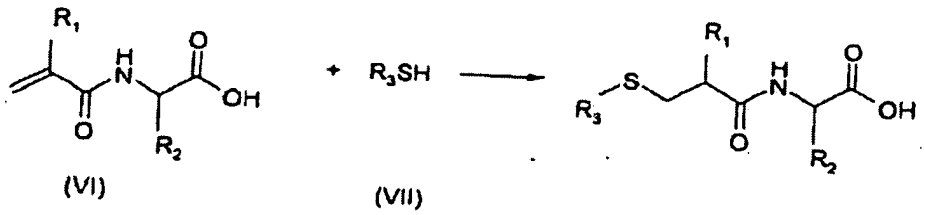
According to a specific embodiment (column 3, lines 25-61), the precursor (IV) is obtained by the following reactions:

(a) coupling reaction:



(V) (VI)

(b) Michaël Addition:



The Michaël addition step disclosed by Greenberg does not involve the use of an unsaturated ester: on the contrary, compound (VI) used by Greenberg in above step (b) is a non esterified unsaturated acid.

Based on the foregoing, the process of Greenberg fails to teach the subject matter of claim 1 (currently amended). Dependent claims 2-16 depend from claim 1 and are not anticipated by Greenberg for at least the same reasons as claim 1 and further for reciting additional features not taught by Greenberg. Therefore, Applicants respectfully request that the rejection to claims 1-16 under 35 U.S.C. § 102(b) be withdrawn.

With regard to the 35 U.S.C. § 103(a) rejection of claims 1-16, the present invention as recited in claim 1 (currently amended) is directed to providing a process for preparing N-(mercaptoacyl)amino acid derivatives of formula (I) which may be exploited on an individual scale. Further, the present process is especially advantageous with regard to the yield of the obtained compounds (see specification, page 5, lines 16-23). The solution proposed by the present inventors comprises preparing compounds of formula (I) by a Michaël addition of an ester of formula (VI) with a thiol of formula (VII), e.g., as recited in claim 4.

As stressed in the application, the present inventors have discovered that this reaction actually leads to a high yield. Unexpectedly, this reaction further provides

compounds of high purity at a low cost (page 5, line 22). Moreover, the inventors have surprisingly evidenced that, when R2 is not a hydrogen atom, the Michaël addition is diastereoselective (specification, page 12, lines 16-32 and page 14, lines 14-21).

The possibilities of synthesizing compounds of formula (I) with a high yield from esters and thiol cannot be regarded as obvious over the teaching of Greenberg which disclose an addition of an acid with a thiol.

In this connection, it should first be stressed that Greenberg does not contemplate the possibility of implementing an ester in the specific Michaël addition reaction disclosed in the cited patents. Thus, one of ordinary skill in the art would have found no motivation or suggestion within Greenberg to modify the disclosed process to replace the acid (V) by a corresponding ester (VI) as recited in claim 1.

Moreover, it should be stressed that, at the time the invention was made, it was known in the art that, in most cases, Michaël additions of thiols onto esters lead to yields which are significantly lower than in the case of addition of acids with thiols.

To further support this specific point, attached is a Rule 132 Declaration by co-inventor Denis Danvy. The Declaration provides results of comparative tests performed with regard to two Michaël additions:

(1) an unsaturated acid (benzylacrylic acid) and a thiol (thioacetic acid); and

(2) a corresponding unsaturated ester (ethyl benzacrylate) and a thiol (thioacetic acid).

These comparative results show that the use of the ester leads to a conversion of only 50%, whereas the use of the acid leads to a conversion of at least 96%.

Based on these results, Greenberg would teach one of ordinary skill in the art who is attempting to achieve a high yield, not to implement an ester instead of an acid, since the skilled artisan would have expected that the use of esters would decrease the yield of the reaction.

Furthermore, the present invention provides further advantages which are not obvious from Greenberg. For example, the enclosed Declaration shows that the Michaël addition of a thiol onto an unsaturated ester does not lead in the general case to a compound of high purity; thus, many sub-products are obtained in the case of the tested reaction of thioacetic acid onto ethyl benzacrylate.

Based on the foregoing discussion, claims 1-16 are not obvious from Greenberg and therefore, Applicants respectfully request that the rejection to claims 1-16 under 35 U.S.C. § 103(a) be withdrawn.

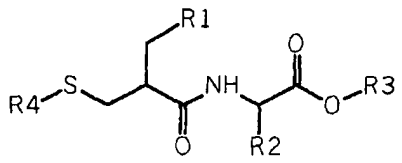
In view of the foregoing, Applicants respectfully submit that the present application is in condition for immediate allowance.

END REMARKS

ATTACHMENT B
Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

1. (Currently Amended) ~~Process~~ A process for preparing a compound of formula (I):



(I)

wherein:

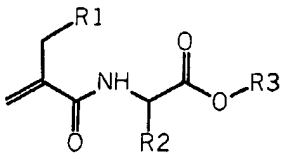
- R1 represents: - a phenyl group; or
  - a 3,4-methylenedioxyphenyl ~~group~~ group;
- R2 represents a hydrogen atom or a lower alkyl group;
- R3 represents ~~a hydrogen atom,~~ a lower alkyl group or a lower phenylalkylene group; and
- R4 represents a linear or branched aliphatic acyl radical or an aromatic acyl radical,

said process comprising ~~a~~ step (B) ~~which consists in~~ performing a ~~Michael~~ Michaël addition of a thioacid of formula (IV):

R4SH (IV)

wherein R4 has the same meaning as in formula (I),

with an α-substituted acrylamide derivative of formula (V):

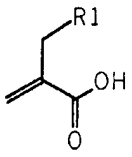


(V)

wherein R1, R2 and R3 have the same meaning as in formula (I).

2. (Currently Amended) ~~Process~~ The process according to claim 1, wherein the group R4 represents an acetyl radical CH_3-CO-, a benzoyl radical C_6H_5-CO- or a pivaloyl radical ~~$(CH_3)_3$-CO-~~ $(CH_3)_3$-CO-.

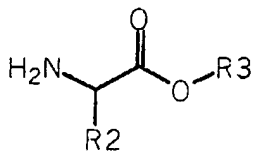
3. (Currently Amended) ~~Process~~ The process according to claim 1, wherein said α-substituted acrylamide derivative of formula (V) is obtained from a step (A), prior to step (B), said step (A) comprising ~~a step consisting in~~ performing the coupling of an acrylic acid of formula (VI):



(VI)

wherein R1 has the same meaning as in formula (I),

with an amino ester of formula (VIII):

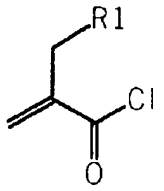


(VIII)

wherein R2 and R3 have the have the same meaning as in formula (I).

4. (Currently Amended) ~~Process~~ The process according to claim 3, wherein ~~said~~ the coupling of the acrylic acid (VI) and of the amino ester (VIII) that is performed in step (A) comprises the successive steps ~~consisting in~~:

(A1) reacting said α-substituted acrylic acid of formula (VI) with an chloro acid so as to obtain an acid chloride of formula (VII):



(VII)

wherein R1 has the same meaning as in formula (I); and

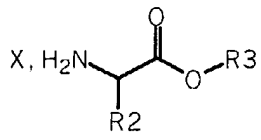
(A2) reacting the acid chloride of formula (VII) thus obtained with said amino ester of formula (VIII), in the presence of a base, so as to achieve the coupling.

5. (Currently Amended) ~~Process~~ The process according to claim 4, wherein the chloro acid used in step (A1) is ~~chosen~~ selected from the group consisting of $SOCl_2$, ClCO-COCl, PCl_3 and PCl_5.

6. (Currently Amended) ~~Process~~ The process according to claim 4, wherein the acid chloride of formula (VII) obtained from step (A1) is subjected to a distillation step before being used in step (A2).

7. (Currently Amended) ~~Process~~ The process according to claim 4, wherein the base used in step (A2) is an organic amine.

8. (Currently Amended) ~~Process~~ The process according to ~~claim 1,~~ claim 4, wherein the amino ester used in step (A2) is introduced in the form of a salt of formula (VIIIa):



(VIIIa)

wherein R2 and R3 have the have the same meaning as in formula (I); and wherein X is chosen from HCl, CH_3SO_3H and 4-methylphenyl-SO_3H.

9. (Currently Amended) ~~Process~~ The process according to claim 4, wherein step (A2) is carried out in the presence of an organic solvent ~~chosen from~~ selected from the group consisting of toluene, dichloromethane, 1,2-dichloroethane, chloroform, N,N-dimethylformamide, 1,4-dioxane, N-methylpyrrolidone, N,N-dimethylacetamide, butyl acetate, ethyl acetate, isobutyl acetate, isopropyl acetate, methyl acetate, propyl acetate and tetrahydrofuran.

10. (Currently Amended) ~~Process~~ The process according to claim 1, wherein compound (V) used in step (B) is a chiral compound wherein R2 denotes a lower alkyl group, said compound (V) being used at least predominantly in its S configuration or at least predominantly in its R configuration.

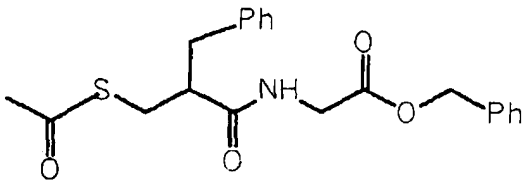
11. (Currently Amended) ~~Process~~ The process according to claim 10, wherein compound (V) is used in its ~~ptically~~ optically pure S form.

12. (Currently Amended) ~~Process~~ The process according to claim 11, wherein compound (V) is prepared by a condensation reaction of an acrylic acid of formula (VI) with an amino ester of formula (VIII) derived from a natural amino acid.

13. (Currently Amended) ~~Process~~ The process according to claim 10, wherein chirality inducers are used in step (B).

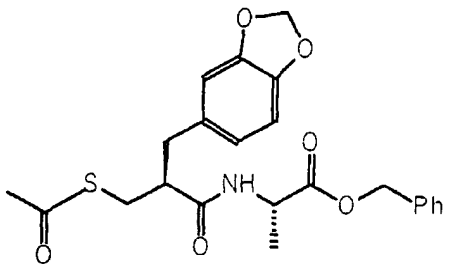
14. (Currently Amended) ~~Process~~ The process according to claim 10, ~~which~~ further ~~comprises~~ comprising, after step (B), a subsequent step (C) of ~~separation of~~ separating the diastereoisomers obtained in step (B).

15. (Currently Amended) ~~Process~~ The process according to claim 1, wherein said obtained compound of formula (I) is benzyl N-(RS)-[2-acetylthiomethyl-1-oxo-3-phenylpropyl]glycinate of formula (II):



(II)

16. (Currently Amended) ~~Process~~ The process according to claim 1, wherein said obtained compound of formula (I) is benzyl N-(S)-[2-acetylthiomethyl-1-oxo-3-(3,4-methylenedioxyphenyl)propyl]-(S)-alaninate of formula (III):



(III)